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021003
BAKER & BOTTS
30 ROCKEFELLER PLAZA
NEW YORK NY 10112

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EXAMINER	
LACOURCIERE,K	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/598,274	Applicant(s) WRAIGHT ET AL.	
	Examiner Karen A. Lacourciere	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,12* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

FILE

DETAILED ACTION

The Examiner would like to express her appreciation to the Applicant for providing a copy of the claims as they will issue in the copending application 09/199,926.

Claim Objections

1. Claim 61 is objected to because of the following informalities: In the last line of the claim, SEQ ID NO:12 has been incorrectly written as "SEQID ID NO:12". Appropriate correction is required.

2. Claim 87 is objected to because of the following informalities: In the first line of the claim, the term "nucleicacid" should be corrected to read "nucleic acid". Appropriate correction is required.

3. Claim 87 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 86. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Although neither claim has been allowed at this time, it is suggested that Applicant cancel either claim to avoid this issue, as the claims are duplicate claims.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 45-60 and 64-75 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 5,929,040. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application would be encompassed by the generic claims of U.S. Patent No. 5,929,040. For example, the instant claims are drawn to methods of treatment using specific antisense sequences and these methods would be encompassed in the generic methods of treatment claimed in U.S. Patent No. 5,929,040.

6. Claims 61-63 and 76-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-36 of copending Application No. 09/199,926. Although the conflicting claims are not identical, they are not

patentably distinct from each other because the instant claims are drawn to nucleic acids and compositions comprising antisense directed to IGFBP-2 or -3 which would be encompassed in the nucleic acids and pharmaceutical compositions of antisense claimed in 09/199,126.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 45-87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 45-60 and 64-87 are indefinite due to the recitation "chemical analogue". One skilled in the art would not know what compounds are encompassed by the term "chemical analogue" because the metes and bounds of this term are unclear. For example, what changes and to what degree can a compound differ from the claimed oligonucleotide and still be considered a "chemical analogue", does the compound need to have the same activity, does the compound

need to be a nucleic acid, does the sequence need to remain the same or can a number of sequence changes be made, etc.

10. Claim 45, and claims dependent on claim 45, are indefinite due to the recitation "and/or other medical disorders". It is unclear how the term "other medical disorders" relates to the claimed methods, since the preamble set forth a method of treating skin cell proliferation and/or inflammation, particularly in the alternative wherein the nucleic acids used in the claimed method are capable of treating only "other medical disorders".

11. Claims 61-63 are indefinite due to the recitation "otherwise interacting". The metes and bounds of the term "otherwise interacting" are unclear and, therefore, one skilled in the art could not determine what nucleic acids are encompassed by these claims.

12. Claims 61-63 are further indefinite due to the recitation "complementary form". It is unclear what the term "complementary form" would encompass, for example, whether the nucleic acid recited must be totally complementary to the SEQ ID NO:'s of the claim or partially complementary.

13. Claim 61 is indefinite because it is unclear whether the claimed nucleic acid is capable of interacting with a complementary form of any one of SEQ ID NO:10, 12, 13, 14, 15, 16, 17, 18,

19 or 20, or if the claimed nucleic acid must be capable of interacting with a complementary form of either SEQ ID NO:10 or each of SEQ ID NO:'s 12-20.

14. Claim 62 is indefinite because it is unclear whether the claimed nucleic acid is capable of interacting with a complementary form of any one of SEQ ID NO:12-20 or if it must be capable of interacting with the complementary form of each of SEQ ID NO:12-20.

15. Claim 63 is indefinite because it is unclear whether the claimed nucleic acid is capable of interacting with a complementary form of any one of SEQ ID NO:12, 13, 14 or 20, or if the claimed nucleic acid must be capable of interacting with a complementary form of either SEQ ID NO:20 or each of SEQ ID NO:'s 12, 13 and 14.

16. Claims 64-75 are indefinite due to the recitation "directed from". It is unclear how an mRNA is "directed from" a gene.

For the purposes of the examination of the instant case, "directed from" has been interpreted to mean "transcribed from".

17. Claim 76 recites the limitation "the mammal". There is insufficient antecedent basis for this limitation in the claim.

18. Claim 84 is indefinite because the claim is written in two sentences and it is unclear whether the claim is drawn to a composition (as suggested by the first sentence) or a method (as suggested by the second sentence).

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 45-60 and 64-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treatment for IGF-I mediated proliferative and/or inflammatory skin disorders in inflamed or proliferating skin, does not reasonably provide enablement for methods of treatment for proliferative and/or inflammatory skin disorders mediated by a growth factor other than IGF-I, nor does it reasonably provide enablement for treatment of skin capable of becoming inflamed or proliferating. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 45-60 and 64-75 are drawn to methods of ameliorating the effects of a proliferative or inflammatory skin disorder in a mammal, including psoriasis, and encompass methods wherein skin capable of proliferation or inflammation. These methods are further drawn to disorders mediated by growth factors other than IGF-I, including wherein the inflammation is mediated by KGF, TGFα, TNFα, IL-1, IL-4, IL-6, IL-8 or bFGF.

The specification provides examples wherein antisense targeted to IGF-I is used to inhibit the expression of IGF-I in cells in culture and wherein antisense targeted to IGF-I is used to ameliorate proliferative and inflammatory skin disorders, including psoriasis, in xenograft skin mouse models wherein effects are ameliorated in skin which exhibits symptoms of psoriasis. There are no examples wherein normal skin is prevented from developing inflammatory or proliferative effects using the claimed methods. Further, there are no examples presented wherein the methods are practiced on proliferative or inflammatory conditions mediated by KGF, TGFα, TNFα, IL-1, IL-4, IL-6, IL-8 or bFGF. Further, the specification has not demonstrated that there is any correlation between the examples presented and proliferative or inflammatory conditions mediated by KGF, TGFα, TNFα, IL-1, IL-4, IL-6, IL-8 or bFGF, nor does it demonstrate that the claimed oligonucleotides would modulate the activity or expression of KGF, TGFα, TNFα, IL-1, IL-4, IL-6, IL-8 or bFGF, either directly or indirectly.

One skilled in the art would not be able to predictably prevent skin cell proliferation or inflammatory skin conditions or treat skin cell proliferation or inflammation mediated by growth factors other than IGF-I using the claimed methods without undue trial and error experimentation.

Such experimentation would include determining what, if any, types skin cell proliferation or inflammation mediated by growth factors other than IGF-I can be treated with the claimed antisense and whether or not any skin cell proliferation or inflammatory skin conditions can actually be prevented using the claimed methods. Given the art recognized unpredictability of antisense methods of treatment (see, for example, Branch, Jen et al., Green et al., Agrawal) , it is unpredictable that one skilled in the art could used the claimed methods to prevent skin cell proliferation or inflammation, or treat conditions mediated by other growth factors, as claimed.

For one skilled in the art to practice the methods of treatment claimed, over the full scope claimed, it would require undue trial and error experimentation beyond the teachings of the instant specification.

Claim Rejections - 35 USC § 102

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

22. Claims 61-63, 76, 78 and 81 are rejected under 35 U.S.C. 102(a) as being anticipated by Wang (WO 99/60855).

Wang discloses a nucleic acid consisting of SEQ ID NO:10, chemical analogues of SEQ ID NO:10, analogues of SEQ ID NO:14 (for example an 18-mer DNA analogue of SEQ ID NO:14) and nucleic acids which hybridize to each of these sequences (see, for example, Example 35 of Wang, especially table 1). Wang further discloses these nucleic acids in a pharmaceutically acceptable carrier. Wang does not disclose these nucleic acids as capable of inhibiting cell proliferation, however, absent evidence to the contrary, this property would be expected to be inherent to the disclosed nucleic acids. Therefore, Wang anticipates claims 61-63, 76, 78 and 81.

23. Claims 61-63, 76, 78 and 81 are rejected under 35 U.S.C. 102(a) as being anticipated by Wang (US Patent No. 5,681,940).

Wang (US Patent No. 5,681,940) discloses a nucleic acid consisting of SEQ ID NO:10, chemical analogues of SEQ ID NO:10, analogues of SEQ ID NO:14 (for example an 18-mer DNA analogue of SEQ ID NO:14) and nucleic acids which hybridize to each of these sequences (see, for example, SEQ ID NO: 2 of Wang (US Patent No. 5,681,940)). Wang (US Patent No. 5,681,940) further discloses these nucleic acids in a pharmaceutically acceptable carrier. Wang (US Patent No. 5,681,940) does not disclose these nucleic acids as capable of inhibiting cell proliferation, however, absent evidence to the contrary, this property would be expected to be

inherent to the disclosed nucleic acids. Therefore, Wang (US Patent No. 5,681,940) anticipates claims 61-63, 76, 78 and 81.

24. Claims 61-63, 76 and 79 are rejected under 35 U.S.C. 102(b) as being anticipated by Baserga et al.(U.S. Patent No. 5,643,788).

Baserga et al. disclose an 18 mer nucleic acid analogue of the instantly claimed SEQ ID NO:12 (SEQ ID NO:4 of Baserga et al.) capable of inhibiting IGF-I mediated cell proliferation, which would hybridize to the complement of the instantly claimed SEQ ID NO:12, and further disclose this nucleic acids in a pharmaceutically acceptable carrier. Therefore, Baserga et al. anticipates claims 61-63, 76 and 79.

25. Claims 61-63, 76 and 79 are rejected under 35 U.S.C. 102(b) as being anticipated by Delafontaine.

Delafontaine discloses a 20-mer DNA analogue of SEQ ID NO:12 (SEQ ID NO:1 of Delafontaine) this nucleic acid would be capable of hybridizing to a complementary form of SEQ ID NO:12. Delafontaine further discloses this oligonucleotide in a pharmaceutically acceptable carrier. The nucleic acid disclosed by Delafontaine would be expected to inherently be capable of inhibiting IGF-I mediated cell proliferation, absent evidence to the contrary. Therefore, Delafontaine anticipates claims 61-63, 76 and 79.

26. Claims 61-63, 76 and 79 are rejected under 35 U.S.C. 102(b) as being anticipated by Low et al. (WO 98/22579).

Low et al. (WO 98/22579) disclose an 18 mer DNA analogue of the instantly claimed SEQ ID NO: 12 (SEQ ID NO:1 of Low et al.), the nucleic acid disclosed by Low et al. would hybridize to a complementary form of the instantly claimed SEQ ID NO:12. Low et al. further disclose their oligonucleotide in a pharmaceutically acceptable carrier. The nucleic acid disclosed by Low et al. would inherently be capable of inhibiting IGF-I mediated cell proliferation. Therefore, Low et al. anticipates claims 61-63, 76 and 79.

27. Claims 61-63, 76 and 79 are rejected under 35 U.S.C. 102(e) as being anticipated by Low et al. (U.S. Patent No. 6,071,891). Low et al. disclose an 18 mer DNA analogue of the instantly claimed SEQ ID NO: 12 (SEQ ID NO:1 of Low et al.), the nucleic acid disclosed by Low et al. would hybridize to a complementary form of the instantly claimed SEQ ID NO:12. Low et al. further disclose their oligonucleotide in a pharmaceutically acceptable carrier. The nucleic acid disclosed by Low et al. would inherently be capable of inhibiting IGF-I mediated cell proliferation. Therefore, Low et al. anticipates claims 61-63, 76 and 79.

28. Claims 45-51, 54, 61-66, 69, 76, 78 and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Werther et al. (reference WO 96/01636 on PTO form 1449, filed March 16, 2001).

Werther et al. disclose methods of treatment for proliferative and inflammatory skin disorders, including psoriasis, using an antisense oligonucleotide of SEQ ID NO:10 (SEQ ID NO:10 of Werther et al.), which is an 18 mer DNA analogue of SEQ ID NO:14, in a pharmaceutically acceptable carrier. This oligonucleotide is capable of hybridizing to a complementary form of SEQ ID NO: 10 or 14. Therefore, Werther et al. anticipates claims 45-51, 54, 61-66, 69, 76, 78 and 81.

29. Claims 61-63 are rejected under 35 U.S.C. 102(b) as being anticipated by Hu et al. (CN1231582A).

Hu et al. disclose a nucleic acid comprising SEQ ID NO:20 (see for example page 2, oligonucleotide identified as PAC83), which would hybridize to a complementary form of SEQ ID NO:18. Therefore, Hu et al. anticipates claims 61-63.

Claim Rejections - 35 USC § 103

30. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

31. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

32. Claims 45-50, 52, 64, 65 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Werther et al. (U.S. Patent No. 5,929,040, cited on PTO form 1449, filed September 25, 2000) in view of Low et al. (U.S. Patent No. 6,071,891), Low et al. (WO 98/22579), Delafontaine, or Baserga et al.

Werther et al. teach methods of treatment for psoriasis and proliferative skin disorders in a mammal, including a human, as claimed, using antisense which inhibits IGF-I. Werther et al. do

not teach their methods of treatment using the specific antisense sequences claimed, or chemical analogues of said sequences.

Low et al. (U.S. Patent No. 6,071,891), Low et al. (WO 98/22579), Delafontaine, or Baserga et al. each teach antisense which inhibits IGF-I, which are chemical analogues of the instantly claimed SEQ ID NO:12.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to ameliorate the effects of psoriasis, or other proliferative or inflammatory skin disorder, in a mammal using the methods taught by Werther et al. using the antisense oligonucleotides taught by Low et al. (U.S. Patent No. 6,071,891), Low et al. (WO 98/22579), Delafontaine, or Baserga et al. because Werther et al. teach that their methods can be practiced with generally any antisense molecule which inhibits IGF-I. One of ordinary skill in the art would have been motivated to practice the methods taught by Werther et al. using the antisense oligonucleotides taught by Low et al. (U.S. Patent No. 6,071,891), Low et al. (WO 98/22579), Delafontaine, or Baserga et al. because Low et al. (U.S. Patent No. 6,071,891), Low et al. (WO 98/22579), Delafontaine, or Baserga et al. each teach that their oligonucleotides are effective inhibitors of IGF-I in cells and are useful as pharmaceuticals directed to treat IGF-I mediated diseases.

Therefore, at the time the instant invention was made, the invention of claims 45-50, 52, 64, 65 and 67 would have been obvious as a whole to one of ordinary skill in the art, absent evidence to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SEAN McGARRY
PRIMARY EXAMINER

Karen A. Lacourciere

May 29, 2001